UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

ASTRAZENECA AB, ASTRAZENECA LP, KBI INC, and KBI-E INC. Plaintiffs and Counterclaim Defendants, v. HANMI USA, INC., HANMI PHARMACEUTICAL CO., LTD., HANMI FINE CHEMICAL CO., LTD, and HANMI HOLDINGS CO., LTD., Defendants and Counterclaim Plaintiffs	Civil Action No. 3: 11-cv-00760-JAP-TJB

DECLARATION OF NIMISH VAKIL, M.D. AGAF, FACG, FACGE

I, Nimish Vakil, M.D., declare:

I. PROFESSIONAL BACKGROUND AND QUALIFICATIONS

1. I am a board-certified gastroenterologist and am also board certified in Internal Medicine. I went to Medical School at the University of Bombay where I earned the M.B.B.S. and M.D. degrees. I completed an Internal Medicine Residency at New York Medical College Affiliated Hospitals (Lincoln Medical and Mental Health Center) in New York City and a Gastroenterology Fellowship at Northwestern University School of Medicine in Chicago, IL. Following my fellowship, I received specialized endoscopy training at the University of Munich, Munich, Germany.

2. I have been teaching gastroenterology for my entire career. I have served on the faculty of the University of Texas, Houston and the University of Rochester in Rochester, New York. Currently, as Clinical Professor of Medicine at the University of Wisconsin School of Medicine and Public Health, I have responsibilities in teaching medical students gastroenterology including the appropriate evaluation of patients with gastro-esophageal reflux disease and their treatment. I lecture medical students and act as their preceptor on Gastroenterology rotations. I also teach trainees in gastroenterology as core faculty of the Aurora Health Care Fellowship in Gastroenterology. I teach gastroenterology fellows the evaluation and management of gastro-esophageal reflux disease and I am in charge of the research training program of fellows. In this capacity, I have supervised among other research studies on the appropriate utilization of proton pump inhibitors in the hospital setting.[1]

[1]Guda NM, Noonan M, Kreiner MJ, Partington S, Vakil N. *Use of intravenous proton pump inhibitors in community practice: an explanation for the shortage?* Am J Gastroenterol. 2004 Jul;99(7):1233-7.

3. Moreover, I have periodically conducted courses on gastroenterology for primary care providers in which we discuss the treatment of gastroenterological disorders including gastro-esophageal reflux disease. As Clinical Associate Professor of Medicine at the Marquette University College of Health Sciences in Milwaukee, Wisconsin, I have been responsible for an annual lecture series in gastroenterology to students who are training to become physician assistants. I have also served as preceptor for their elective clinical rotation in gastroenterology. In this capacity, I taught the pathophysiology and treatment of gastro-esophageal reflux disease to physician assistant students. I have given more than 200 invited lectures throughout the world and been a regular participant in national and international educational meetings concerning gastroenterology, with a particular focus and expertise in gastro-esophageal reflux disease ("GERD") and complications of acid reflux disease. For example, I have lectured at national meetings of Gastroenterology societies in Argentina, Brazil, Chile, China, Japan, Singapore, Indonesia, Russia, UK, France and a number of other countries.

4. I have had extensive involvement with clinical research throughout my career and continue to maintain a very active role in research. This involvement includes research studies in the field of reflux disease, dyspepsia and Helicobacter pylori infection. For example, in the area of reflux disease, I have performed studies that evaluate the impact of combining H_2 receptor antagonists with proton pump inhibitor therapy.[2] I have performed studies on the outcome of surgery for the management of reflux disease.[3] I have evaluated the impact of proton pump

[2] Vakil N, Guda N, Partington S. The effect of over-the-counter ranitidine 75 mg on night-time heartburn in patients with erosive oesophagitis on daily proton pump inhibitor maintenance therapy. Aliment Pharmacol Ther. 2006 Mar 1;23(5):649-53.

[3] Vakil N, Kirby R, Shaw M. Clinical effectiveness of laparoscopic fundoplication in a US community. Am J Med 2003 Jan;114(1):1-5

inhibitors on complications such as a stricture.[4] I have performed studies on the impact of GERD on sleep disorders.[5] I also have consulted on the design of clinical trials, including trials to support regulatory approval. I have served as a consultant for the design of trials of acid inhibitors for the treatment of GERD and have served as a principal investigator for studies on novel mechanisms for treating reflux disease (inhibition of transient lower esophageal sphincter relaxations)[6] and in the design of trials for functional dyspepsia and GERD.[7] In this role, I have appeared as an external consultant in meetings with the FDA to discuss trial design and endpoints for clinical trials.[8]

5. I also have led an international consensus group with members from 18 countries that defined and classified reflux disease and provided a definition and classification that are novel, patient-centered, and global in perspective.[9] I have co-authored studies that examine how proton pump inhibitors are used in clinical practice.[10] I have performed meta-analyses of trials,

---

[4] Guda N, Vakil N. Proton pump inhibitors and the time trends for esophageal dilation. Am J Gastroenterol. 2004 May;99(5):797-800.

[5] Guda N, Partington S, Vakil N. Symptomatic gastro-oesophageal reflux, arousals and sleep quality in patients undergoing polysomnography for possible obstructive sleep apnoea. Aliment Pharmacol Ther. 2004 Nov 15;20(10):1153-9.

[6] Vakil NB, Huff FJ, Bian A, Jones DS, Stamler D. Arbaclofen placarbil in GERD: a randomized, double-blind, placebo-controlled study. Am J Gastroenterol. 2011 Aug;106(8):1427-38.

[7] Dent J, Kahrilas PJ, Vakil N, Van Zanten SV, Bytzer P, Delaney B, Haruma K, Hatlebakk J, McColl E, Moayyedi P, Stanghellini V, Tack J, Vaezi M. Clinical trial design in adult reflux disease: a methodological workshop. Aliment Pharmacol Ther. 2008 Jul;28(1):107-26.

[8] Vakil N, Laine L, Talley NJ, Zakko SF, Tack J, Chey WD, Kralstein J, Earnest DL, Ligozio G, Cohard-Radice M. Tegaserod treatment for dysmotility-like functional dyspepsia: results of two randomized, controlled trials. Am J Gastroenterol. 2008 Aug;103(8):1906-19.

[9] Vakil, N, van Zanten, S., Kahrilas P, Dent J & Jones R. The Montreal Definition and Classification of Gastroesophageal Reflux Disease: A Global Evidence-Based Consensus. American Journal of Gastroenterology 2006;101(8):1900-1920.

[10] Guda N, Noonan M, Kreiner M, Partington S, Vakil N. Use of intravenous proton pump inhibitors in community practice: an explanation for the shortage. Am J Gastroenterol. 2004 Jul;99(7):1233-7. An editorial accompanies this paper.

including a meta-analysis on the efficacy of PPIs for laryngeal symptoms attributed to GERD.[11] I have also performed cost-effectiveness studies that evaluate the cost and effectiveness of different alternatives for the management of gastroenterological disorders.[12, 13] As set forth in my CV, which is attached as Exhibit A, I have authored or co-authored 221 papers, including papers which have been published in the *New England Journal of Medicine*, *Annals of Internal Medicine*, *Journal of the American Medical Association* and the *American Journal of Medicine*, as well as in leading journals in the field of gastroenterology, such as *Gastroenterology* and the *American Journal of Gastroenterology* and *Gut*.[14, 15, 16, 17]

6. I am familiar with the methods of evidence-based medicine and have received training in meta-analysis and cost analysis, including the Cochrane courses on meta-analysis. I have performed several systematic reviews, meta-analyses and cost-effectiveness analyses, which have been published in the peer-review literature.[18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29] I also have

---

[11] Gatta L, Vaira D, Sorrenti G, Zucchini S, Sama C, Vakil N. Meta-analysis: the efficacy of proton pump inhibitors for laryngeal symptoms attributed to gastro-esophageal reflux disease. Aliment Pharmacol Ther 2007 Feb 15;25(4):385-92.

[12] Vakil N. The cost-effectiveness of treating GERD. Eur J Gastroenterol and Hepatol 2001;13:S10-3

[13] Vakil N, Ashorn M. Cost-effectiveness of non-invasive testing and treatment strategies for H pylori infection in dyspeptic children. Am J Gastroenterol 1998;93:562-8.

[14] Vakil N, Schwartz S, Buggy B, Brummitt C, Kherellah M, Letzer D, Gilson I, Jones P. Biliary cryptosporidiosis in people with HIV infection following the waterborne outbreak of cryptosporidium infection. New Engl J Med, 1996;334:19-23.

[15] Talley N, Vakil N, Ballard C, Fennerty B. Effect of eradicating Helicobacter pylori in patients with non-ulcer dyspepsia. New Engl J Med 1999;341:1106-11..

[16] Moayyedi P, Talley NJ, Fennerty MB, Vakil N. Can the clinical history distinguish between organic and functional dyspepsia? JAMA. 2006 Apr 5;295(13):1566-76.

[17] Vaira D, Zullo A, Vakil N, Gatta L, Ricci C, Perna F, Hassan C, Bernabucci V, Tampieri A, Morini S. Sequential therapy versus standard triple-drug therapy for Helicobacter pylori eradication: a randomized trial. Ann Intern Med. 2007 Apr 17;146(8):556-63.

[18] Moayyedi P, Talley NJ, Fennerty MB, Vakil N. Can the clinical history distinguish between organic and functional dyspepsia? JAMA. 2006 Apr 5;295(13):1566-76.

[19] Inadomi J, Sampliner R, Lagergren J, Lieberman D, Fendrick M, Vakil N. Screening and Surveillance for Barretts esophagus in High-Risk Populations: A Cost-Utility Analysis. Ann Intern Med 2003 Feb 4;138(3):176-86.

participated in evidence based training programs for gastroenterologists in clinical practice. In 2010 and in 2011, I served on the American Gastroenterological Association's review panel for meta-analyses being submitted to the annual meeting of the association. I have reviewed meta-analyses and systematic reviews submitted for publication for a number of journals including *Gut*, *American Journal of Gastroenterology* and *Annals of Internal Medicine*. I regularly teach medical students concerning literature searches, publication bias, and meta-analysis, and since 1993, I have conducted a regular journal club for gastroenterology trainees where the literature is evaluated using evidence-based medicine principles. Therefore I am qualified to comment on literature searches, publication bias, meta-analysis and related topics concerning the review and analysis of scientific and medical literature.

---

[20] Ford AC, Talley NJ, Veldhuyzen Van Zanten SJ, Vakil NB, Simel DL, Moayyedi P. Will the history and physical examination help establish that irritable bowel syndrome is causing this patient's lower gastrointestinal tract symptoms? JAMA. 2008 Oct 15;300(15):1793-805.

[21] Moayyedi P, Delaney BC, Vakil N, Forman D, Talley NJ. The efficacy of proton pump inhibitors in nonulcer dyspepsia: a systematic review and economic analysis. Gastroenterology. 2004 Nov;127(5):1329-37.

[22] Spiegel BM, Ofman JJ, Woods K, Vakil NB. Minimizing recurrent peptic ulcer hemorrhage after endoscopic hemostasis: the cost-effectiveness of competing strategies. Am J Gastroenterol. 2003 Jan;98(1):86-97.

[23] Spiegel BM, Ofman JJ, Woods K, Vakil NB. Minimizing recurrent peptic ulcer hemorrhage after endoscopic hemostasis: the cost-effectiveness of competing strategies. Am J Gastroenterol. 2003 Jan;98(1):86-97.

[24] Vakil N, Rhew D, Soll A. Ofman J. The Cost-Effectiveness of Diagnostic Testing Strategies for H. Pylori. Am J Gastroenterol 2000;95:1691-8.

[25] Rubenstein JH, Vakil N, Inadomi JM. The cost-effectiveness of biomarkers for predicting the development of oesophageal adenocarcinoma.Aliment Pharmacol Ther. 2005 Jul 15;22(2):135-46.

[26] Moayyedi P, Delaney BC, Vakil N, Forman D, Talley NJ. The efficacy of proton pump inhibitors in nonulcer dyspepsia: a systematic review and economic analysis. Gastroenterology. 2004 Nov;127(5):1329-37.

[27] Vakil N, Moayyedi P, Fennerty MB, Talley NJ. Limited value of alarm features in the diagnosis of upper gastrointestinal malignancy: systematic review and meta-analysis.Gastroenterology. 2006 Aug;131(2):390-401.

[28] Gatta L, Vaira D, Sorrenti G, Zucchini S, Sama C, Vakil N.Meta-analysis: the efficacy of proton pump inhibitors for laryngeal symptoms attributed to gastro-oesophageal reflux disease.Aliment Pharmacol Ther. 2007 Feb 15;25(4):385-92.

[29] Vakil N, Ryden-Bergsten T, Bergenheim K. Systematic review: patient-centred endpoints in economic evaluations of gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2002 Aug;16(8):1469-80.

7. I have held a number of leadership positions in various gastroenterology societies. I have served as Chairman of the Practice Parameters Committee of the American College of Gastroenterology, as a member of the Research Committee of the American Society of Gastrointestinal Endoscopy, a member of the research committee of the American College of Gastroenterology, Chairman of the ad hoc Committee on networking of the American Society of Gastrointestinal Endoscopy and a member of the Global Guidelines Committee of the World Organization of Gastroenterology. I have served as a member of the publications committee of the American College of Gastroenterology. I also currently serve on the editorial boards of several journals: *Alimentary Pharmacology and Therapeutics*, *Evidence-based Gastroenterology*, *Folia Gastroenterologica*, *Best Practice and Research in Gastroenterology*. I was Associate Editor of the *American Journal of Gastroenterology* from 2003-2013 and in this capacity regularly (approximately weekly) evaluated and discussed papers with my co-editors regarding the treatment of gastrointestinal disorders. I am currently the U.S. Editor of *Endoscopy*, the official journal of the European Society of Gastrointestinal endoscopy and in this capacity regularly receive papers for potential publication, manage their peer-review and make decisions regarding their suitability for publication. I am therefore familiar with the process of selection and review of research papers for publication. I am an active reviewer for 12 medical journals at the present time.

8. In addition, I co-author content for *UptoDate*, an on-line resource supported by the American Gastroenterological Association, used by physicians on recommendations for upper gastrointestinal disorders. I also serve on advisory boards to organizations that are devoted to gastrointestinal disease, including the Advisory Board of the International Foundation

for Functional Gastrointestinal Disorders, a patient organization for individuals with irritable bowel syndrome, dyspepsia, functional heartburn and other disorders.

9. I was President of a private practice (Digestive Disease Specialists of Wisconsin) and in that role negotiated contracts with managed care and developed practice managed plans. I served on the Gastroenterology advisory board for Anthem (formerly Blue Cross of Milwaukee WI). I have served as a reviewer for United Health Care for cases that did not meet criteria for approval of certain procedures in which the decision was appealed by physicians or patients.

10. I have expertise in how treatments are selected and used in clinical practice. In addition to my research studies related to studies in clinical practice settings described above, at a national level, I have been a member and also the Chairman of the Practice Parameters Committee of the American College of Gastroenterology, a committee which develops practice management guidelines for the management of gastroenterological disorders. I have served on an international committee that develops guidelines for use around the world. I have also co-authored national guidelines for the treatment of gastroenterological disorders. For example, I co-authored the American College of Gastroenterology guidelines on treatment of dyspepsia, the World organization of Gastroenterology guideline on Helicobacter pylori, and the Asia Pacific consensus on GI bleeding .[30,31, 32, 33] I was also a member of the American Gastroenterological Association's eight-member expert panel that generated a practice guideline for reflux disease,

[30] Talley NJ, Vakil N. Practice Parameters Committee of the American College of Gastroenterology. Guidelines for the management of dyspepsia. Am J Gastroenterol. 2005 Oct;100(10):2324-37.

[31] World Gastroenterology Organisation. World Gastroenterology Organisation Global Guideline: Helicobacter pylori in developing countries. J Clin Gastroenterol. 2011 May-Jun;45(5):383-8.

[32] Talley NJ, Vakil NB, Moayyedi P. American gastroenterological association technical review ont eh evaluation of dyspepsia. Gastroenterology. 2005 Nov; 129(5):1756-80.

[33] Sung JJ, Chan FK, Chen M, Ching JY, Ho KY, Kachintorn U, Kim N, Lau JY, Menon J, Rani AA, Reddy N, Sollano J, Sugano K, Tsoi KK, Wu CY, Yeomans N, Vakil N, Goh KL. Asia-Pacific Working Group consensus on non-variceal upper gastrointestinal bleeding. Gut. 2011 Sep;60(9):1170-7.

entitled "Improving the Management of GERD: evidence-based therapeutic strategies.[34] I have served as one of two U.S. representatives on the Maastricht European Consensus guidelines on *H. pylori* that form the basis of all international guidelines.[35] I represented the USA at the last consensus conference in Florence Italy in November 2010. I have participated in invited conferences on *H. pylori* at the National Institute of Health in Washington DC. I have been an invited expert on the Asia Pacific consensus on gastrointestinal bleeding.

11. From 1993-2009, I was in private clinical practice with affiliations to the University of Wisconsin School of Medicine and Public Health in Madison, Wisconsin, and the Marquette University College of Health Sciences in Milwaukee, Wisconsin. I am currently a full-time gastroenterologist at the Aurora Wilkinson Clinic, a part of Aurora Health Care. As a clinician, I see patients in consultation at least 5 days a week and perform endoscopic procedures 5 days a week. As a gastroenterologist, I am frequently asked to evaluate patients who have tried and failed to respond to one or more PPIs for treatment of their GERD, as well as patients with the most severe cases of GERD and complications of GERD. In 2009 and again in 2010,2011 and 2013, I was elected to Best Doctors in America by my peers. In 2011,2012 and 2013 I was also selected by Marquis Who's Who for inclusion in their reference in Medicine and Health Care for 2011-2012. In 2009, I was featured in the *New York Times* in an interview with the

[34] Peterson W and the American Gastroenterological Association Consensus Development Panel. Improving the Management of GERD: evidence based therapeutic strategies. Monogram published by the American Gastroenterological Association. Available on-line at: http://www.gastro.org/user-assets/Documents/GERDmonograph.pdf.

[35] Malfertheiner P, Megraud F, O'Morain C, Bazzoli F, El-Omar E, Graham D, Hunt R, Rokkas T, Vakil N, Kuipers EJ. Current concepts in the management of Helicobacter pylori infection: the Maastricht III Consensus Report. Gut. 2007 Jun;56(6):772-81

expert on *H. pylori* entitled *Holding Back the Ulcer Bug* (*available at* http://www.nytimes.com/ref/health/healthguide/esn-ulcers-expert.html).

12. Based on my training; my clinical practice; my experience teaching medical students, physician assistants, internal medicine residents, and fellows in gastroenterology; and my extensive involvement in research and guidelines concerning treatment of gastroenterological disorders, I feel qualified to speak to standards of care, best practice strategy, criteria on which prescribing physicians select gastroenterological treatments they use in their clinical practice, the qualities and relative benefits of the various treatment options for GERD and other acid-related conditions, and the studies and other data supporting the use of those treatment options.

13. A true and correct copy of my curriculum vitae is attached as Exhibit A.

II. CLINICAL BACKGROUND

A. What Is Gastroesophageal Reflux Disease (GERD)

14. GERD develops when the reflux of stomach contents into the esophagus causes troublesome symptoms and/or complications. The disorder, which is increasing in prevalence, is primarily caused by abnormal regulation of the sphincter muscle at the lower end of the esophagus. The sphincter muscle opens to allow food to enter the stomach and then closes to prevent stomach contents from refluxing back into the esophagus. In a patient with GERD, the sphincter muscle operates abnormally and permits the acidic stomach content to reflux up into the esophagus. Unlike the stomach, the esophagus is not equipped to withstand acid, and the reflux of stomach acid up into the relatively delicate and unprotected tissue of the esophagus is frequently uncomfortable and painful.

15. The most common symptom of GERD is frequent and persistent heartburn. Some patients also may experience regurgitation of gastric contents into the mouth and difficulty

swallowing. Reflux disease can also cause disorders outside the esophagus (extra-esophageal disorders). These disorders include laryngitis, asthma, chest pain and dental erosions.

16. GERD is a very common disorder. In the US alone, 65% of the total adult population experiences heartburn at some point in their life. It is also estimated that GERD affects 10-15% of the population of the western world at any one time. It has also been reported that, in Western populations, 40% of patients report that they experience symptoms on a monthly basis and 7% on a daily basis36.

17. Carefully performed studies have repeatedly shown that GERD can have a major impact on a patient's quality of life, including the ability to sleep, work and eat. Mild symptoms that occur twice a week or severe symptoms that occur just once a week are associated with a measurable decrease in the quality of life. I also know from my own experience with patients that, at its worst, GERD is a debilitating chronic disorder that affects quality of life to an enormous extent. I have seen many patients in consultation who report almost unbearable symptoms. Some have to spend almost every night sitting upright in a chair, trying to sleep in that position, because they are unable to sleep lying down as their symptoms become intolerable when they do.

18. It is also important to note in this context that severe GERD is extremely prevalent. When we conduct clinical trials in large groups of patients with esophagitis, we generally see that one third of all untreated patients come to us presenting severe disease. Thus, as an illustration of this, if, say, 10% of the European population has GERD, of which one third (33%) has disease at the severe end of the spectrum, I would expect this to amount to in the region of between 3% and 4% of the entire European population at any one time.

[36]Kulig *et al*, "*Quality of life in relation to symptoms in patients with gastro-oesophageal reflux disease – an analysis based on the ProGERD initiative*", *Aliment. Pharmacol. Ther.*, 2008; 18:767-76 (Attachment 5)

19. For patients with severe GERD, there is also a greater risk of development of organic diseases. When reflux occurs, the lining of the esophagus is injured, which may result in esophagitis. The refluxed contents can cause visible damage to the lining of the esophagus by creating breaks in the skin lining the esophagus. These breaks are referred to as erosions; when a person has these breaks, the condition is referred to as erosive esophagitis (EE).

20. EE is not present in all patients with GERD, but it is a complication of GERD. EE cannot be diagnosed by symptoms alone, and symptoms do not correspond to the severity of the disease in the individual patient. EE is instead diagnosed by endoscopy. Erosions in the esophagus are graded based on severity using an international classification called the Los Angeles Classification. There are four grades of severity in the Los Angeles Classification corresponding to the severity of injury seen at endoscopy: Grade A: One or more mucosal breaks confined to the mucosal folds, each not more than 5 mm in maximum length; Grade B: One or more mucosal breaks confined to more than 5 mm in maximum length but not continuous between the tops of the mucosal folds; Grade C: Mucosal breaks that are continuous between the tops of 2 or more mucosal folds but which involve less than 75% of the circumference of the esophagus; Grade D: Mucosal breaks which involve at least 75% of the esophageal circumference.

21. There is a correlation between the amount of acid entering the esophagus and the degree of esophagitis, providing an approximate correlation between the severity of the abnormalities in regulation of the esophageal sphincter and the abnormalities seen at endoscopy. Published data suggest that the severity of EE is associated with the extent and time that the esophageal tissue is exposed to refluxed stomach acid, with greater acid exposure resulting in more severe damage to esophageal tissue. The degree of acidity of the refluxate is measured in

terms of pH. Stomach refluxate that has a pH less than 4 is associated with esophageal injury as well as with acid-related symptoms, like chronic heartburn.

22. Other serious, long-term complications of GERD include esophageal bleeding, esophageal stricture resulting in obstruction, ulcers, and a pre-cancerous change in the esophagus called Barrett's esophagus and esophageal cancer. Chronic reflux disease is the leading risk factor for adenocarcinoma of the esophagus, a cancer with a high mortality rate and a growing incidence. Effective treatment of EE by complete healing of the damaged tissue, and then maintaining that healing, generally is recommended as a possible means of avoiding many of these serious complications.

B. Treatment of GERD

23. Only 30 years ago, the treatment options for patients suffering from GERD were limited and frequently unsatisfactory. The primary treatment was administration of antacids to neutralize stomach acid, but this treatment typically offered only temporary relief. The alternative was surgery. In another procedure, a fundoplication, the surgeon wrapped a portion of the patient's stomach around the junction of the patient's esophagus to reinforce the natural barrier between the stomach and the esophagus. These surgeries, while effective in reducing the experience of heartburn pain or the amount of refluxate, carried the risk of significant complications.[37]

24. Medical therapy for treatment of reflux disease has evolved from the frequent use of antacids to drugs that decrease acid secretion. These agents decrease the volume of acid secretion in the stomach and thereby decrease the amount of material that refluxes up into the

[37] Vakil N, Shaw M, Kirby R. Clinical effectiveness of laparoscopic fundoplication in a U.S. community. Am J Med. 2003 Jan;114(1):1-5.

esophagus. By decreasing acid production, the acidity of the refluxate is also decreased. Any material that refluxes up into the esophagus is therefore less injurious than it would have been without treatment. Treatment through acid inhibition results in an improvement in symptoms and healing of erosions in the esophagus.

25. Two major classes of acid-inhibitory drugs are widely used for the treatment of reflux disease. The first class is called Histamine 2 receptor antagonists (H_2RAs), which includes drugs such as ranitidine (Zantac) and famotidine (Pepcid). Some of these drugs are available by prescription, and some are also available over-the-counter (e.g., Zantac, Pepcid, Tagamet, and combination drugs such as Pepcid Complete, which combines an H_2RA and an antacid). Generic versions of several H_2RAs are also available (e.g., ranitidine (generic version of Zantac), cimetidine (generic version of Tagamet)).

26. The second class of acid-inhibitory drugs is proton pump inhibitors (PPIs). A meta-analysis of many trials published on the efficacy of these two classes of drugs has shown that proton pump inhibitors are more effective than H_2RAs in the treatment of esophagitis.[38]

27. Prilosec® (omeprazole) was the first PPI on the market, followed by Prevacid® (lansoprazole), Aciphex® (rabeprazole), Protonix® (pantoprazole), Nexium® (esomeprazole), and Dexilant® (Dexlansoprazole).[39] Generic versions of omeprazole, pantoprazole, and lansoprazole are now available. In addition, omeprazole is available over-the-counter as Prilosec OTC, which is FDA-approved for treatment of frequent heartburn as part of a 14-day course of therapy, after which consultation with a doctor is recommended; omeprazole is also is available over-the-counter in a generic version. Lansoprazole also is available over-the-counter as

[38] Khan M, Santana J, Donnellan C, Preston C, Moayyedi P. Medical treatments in the short term management of reflux oesophagitis. Cochrane Database Syst Rev. 2007 Apr 18;(2):CD003244. Review.

[39] Another branded product called Zegerid is an immediate release preparation of omeprazole combined with bicarbonate, approved at 20 mg for healing EE.

Prevacid® 24HR. Pantoprazole also is available as a generic drug. Each proton pump inhibitor has been approved by the FDA for different indications and at different recommended doses for GERD-related indications. For example the highest approved doses for healing of erosive esophagitis are 20 mg for Prilosec® (omeprazole), 20 mg for Aciphex®, 30 mg for Prevacid®, 40 mg for Protonix® (pantoprazole), 40 mg for Nexium®, and 60 mg for Dexilant® (dexlansoprazole).

28. Notwithstanding the significant benefits patients and doctors enjoyed with omeprazole over prior therapies, not all patients are helped with omeprazole (or other PPIs). In a Gallup poll in the USA, only 49% of patients were completely satisfied with GERD therapy.[40] Similar data were reported in a US study of 11,064 users of medication for heartburn in the USA. In that study, conducted prior to the availability of Nexium®, only 46% of heartburn sufferers were completely satisfied with their therapy.[41] Professor Tytgat wrote about the unmet needs of patients with GERD.[42] He suggested that full 24-hour control of gastric acid secretion should be available with medical therapy to fine-tune acid suppressant therapy to the individual clinical needs. He also pointed out that "for ordinary GERD, full symptom control and patient satisfaction is often lacking, necessitating additional over-the-counter medication for control of remaining symptoms." He also suggested that the available PPIs were suboptimal for "on-demand" therapy in Non-Erosive Reflux Disease (NERD)/GERD. Some of these unmet needs were addressed by the creation of Nexium®.

---

[40] Shaker R, Castell DO, Schoenfeld PS, Spechler SJ. Nighttime heartburn is an under-appreciated clinical problem that impacts sleep and daytime function: the results of a Gallup survey conducted on behalf of the American Gastroenterological Association. Am J Gastroenterol. 2003 Jul;98(7):1487-93.

[41] Crawley J, Schmitt C. How satisfied are chronic heartburn sufferers with their prescription medications?Results of the patient unmet needs study. J Clin Outcomes Management 2000;7:29-34.

[42] Tytgat GNJ. Are there unmet needs in acid suppression? Best Practice & Research Clinical Gastroenterology Volume 18, Supplement, 2004, Pages 67-72.

29. It thus is clear that a substantial number of patients were dissatisfied with existing treatment options, including omeprazole. In addition, in assessing whether Nexium® offers advantages over omeprazole, one needs to evaluate the room available for improvement in comparison to omeprazole, one needs to evaluate the results previously obtained with omeprazole. For example, the FDA approved labeling for omeprazole states that the healing rate for erosive esophagitis in its approved dose of 20 mg/day was 74%.[43] Therefore any new drug that hopes to achieve better results has only 26% room for improvement. Similarly the FDA approved label for omeprazole states that complete relief of GERD symptoms was achieved in 84% of patients in the erosive esophagitis trials leaving only 16% of patients who could improve compared to existing treatment with a new agent.[44]

C. Nexium®

30. Nexium® (esomeprazole magnesium) addresses the patient needs that are left unmet by omeprazole by improving acid inhibition, leading to more predictable and better acid control and therefore improved outcomes in patients, as is described below.

31. Nexium® and omeprazole are different drugs, with different pharmacokinetic and pharmacodynamic properties. By way of background, many drugs are a mixture of two molecules**,** called isomers, that have the same molecular formula, but have a different arrangement of the atoms in space. These isomers are mirror images of each other, called enantiomers. The mixture is called racemic when there are equal amounts of the two compounds. Omeprazole is an example of a racemic mixture of two mirror-image molecules, called enantiomers: S-omeprazole and R-omeprazole.

[43]http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory. Accessed October 9, 2011.

[44]http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory accesed October 9, 2011

32. Each isomer of omeprazole can produce acid inhibition. However, the S-isomer, esomeprazole, is metabolized more slowly than the R-isomer and omeprazole (the mixture). The S-isomer therefore produces higher plasma concentrations for longer and, as a result, inhibits gastric acid production more effectively and for longer. Thus, esomeprazole has the pharmacological properties of a more effective form of treatment for disorders related to gastric acid secretion. As described below, clinical studies have confirmed the anticipated increased efficacy.

33. Although Nexium® and omeprazole are related compounds, they plainly are not the "same," as their metabolism makes clear.[45, 46] The R-isomer of omeprazole and esomeprazole (the S-isomer) are both metabolized by the liver. After passing through the liver a portion of the active drug is metabolized and inactivated (all metabolites of omeprazole and esomeprazole are inactive), while the remaining molecules are circulated in the bloodstream to the parietal cells of the stomach lining, where they bind to the acid secretory pumps to suppress the production of stomach acid. The more quickly the molecules are metabolized, the more quickly they are inactivated, and fewer molecules remain to circulate to the stomach to act to suppress the production of stomach acid.[47]

34. Omeprazole and its isomers are metabolized and inactivated by two metabolic pathways known as the cytochrome P450 enzymes CYP2C19 and CYP3A4. CYP2C19 is a more rapidly metabolizing pathway than CYP3A4. The metabolism of R-omeprazole is more

[45] Creutzfeldt W. Chiral switch, a successful way for developing drugs: example of esomeprazole. Z Gastroenterol 2000; 38: 893–7.

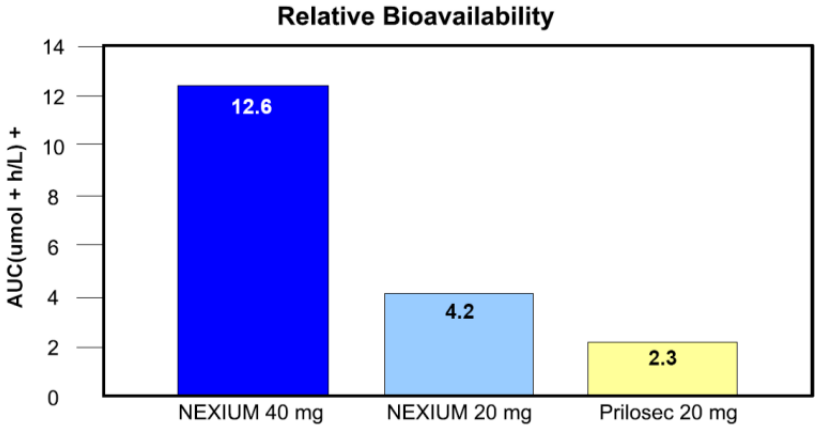
[46] Andersson T, Hassan-Alin M, Hasselgren G, Röhss K, Weidolf L. Pharmacokinetic studies with esomeprazole, the (S)-isomer of omeprazole. Clin Pharmacokinet 2001; 40: 411–26.

[47] Dent J. Review article: pharmacology of esomeprazole and comparisons with omeprazole. Aliment Pharmacol Ther 2003; 17(Suppl. 1): 5-9.

dependent on the CYP2C19 pathway, whereas a substantial portion of esomeprazole is metabolized by the slower CYP3A4 pathway. As the CYP3A4 metabolizes more slowly, less esomeprazole is metabolized on each pass through the liver and more unmetabolized esomeprazole reaches the parietal cells of the stomach than in the case of omeprazole.

35. Because esomeprazole is metabolized at a lower rate, it results in higher plasma levels – also described as greater bioavailability – of esomeprazole, which is frequently measured as the "area under the curve," or "AUC."[48] In the study displayed below, after 5 days of dosing, the bioavailability – measured as the AUC – of esomeprazole (Nexium®) 20 mg was almost twice that of omeprazole (Prilosec) 20 mg, while the bioavailability of 40 mg esomeprazole was more than 5 times greater than 20 mg omeprazole:[49]

Figure 13



[48] Andersson T, Rohss K., Bredberg E., Hassan-Alin T. Pharmacokinetics and pharmacodynamics of esomeprazole, the S-isomer of omeprazole. Aliment Pharmacol Ther 2001; 15(10): 1563–1569.

[49] Lind T, Rydberg L, Kylebäck A, Jonsson A, Andersson T, Hasselgren G, Holmberg J, Röhss K. Esomeprazole promotes improved acid control vs. omeprazole in patents with symptoms of gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2000 Jul; 14 (7): 861-7.

36. There was less inter-patient variability in AUC and gastric acid suppression with Nexium® than with omeprazole in this study.[50]

37. The metabolism of esomeprazole is not only slower but more consistent in different individuals than the metabolism of omeprazole or its R-isomer.[51] First, the CYP2C19 pathway has more genetic variability than the CYP3A4 pathway. In about 15% of the Asian population and about 3% of the Caucasian population, the CYP2C19 system is absent. Because the metabolism of omeprazole occurs so significantly in the CYP2C19 pathway, there is corresponding variation among individual patients in how much omeprazole reaches the target cells.

38. Second, Nexium® maintains the area under the curve (AUC) in a therapeutic range in a larger proportion of patients. An AUC greater than 2 (uμol + h/L) provides peak acid inhibition; once the AUC is higher than 2, there is almost complete inhibition of acid secretion.[52, 53] The AUC with Nexium® 20 mg and 40 mg has been shown to be consistently above 2 compared to omeprazole 20 mg.[54] In a study by Lind et al., the steady state AUC for omeprazole 20 mg in 36 patients with GERD ranged from 1.83 to 3.00 [mean 2.34]; with Nexium® 20 mg, the range was 3.27 to 5.35 [mean 4.18], and with Nexium® 40 mg, the range was 9.89 to 16.17 [mean 12.64].[55] Therefore, the AUC with Nexium® was consistently well above the peak acid

---

[50] *Id*.

[51] Kendall MJ. Review article: esomeprazole – the first proton pump inhibitor to be developed as an isomer. Aliment Pharmacol Ther 2003; 17(Suppl. 1): 1– 4.

[52] Andersson et al. (2001), *supra* n. 48.

[53] Lindberg P, Keeling D, Fryklund J, Andersson T, Lundborg P, Carlsson E. Review article: esomeprazole – enhanced bio-availability, specificity for the proton pump and inhibition of acid secretion. Aliment Pharmacol Ther 2003; 17: 481-488.

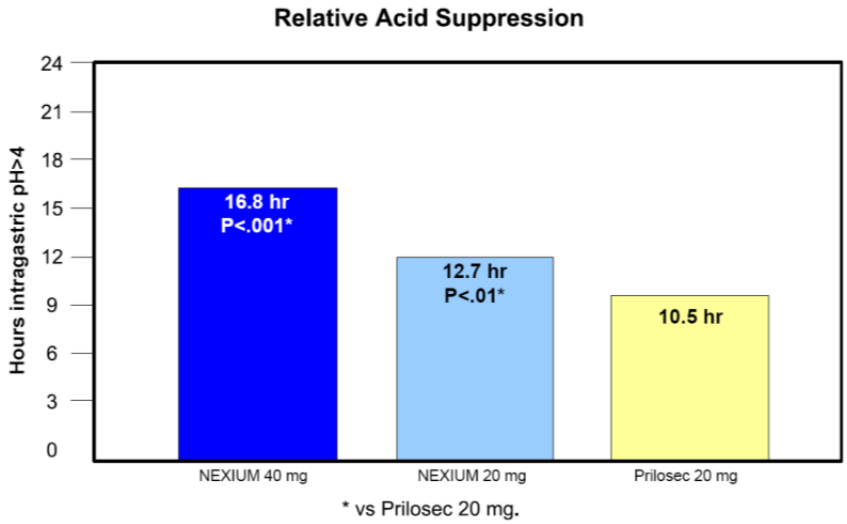
[54] Lind et al. (2000), *supra* n.49.

[55] Lind et al. (2000), *supra* n.49.

inhibitory AUC threshold of 2. In addition, there was less inter-patient variability in AUC with Nexium®.[56]

39. These differences in metabolism provide one explanation for the greater acid suppression seen with Nexium®. For example, in a double-blind, crossover study, 40-mg and 20-mg Nexium® maintained mean gastric pH higher than 4, an important marker (*see infra*), for 16.8 hours ($P < 0.001$) and 12.7 hours ($P < 0.01$), respectively, versus 10.5 hours for omeprazole, as displayed below:[57]

Figure 14



40. Compared with the 24-hour mean gastric pH for omeprazole (3.6), mean pH levels were significantly higher for Nexium®: 40 mg (4.9, $P < 0.001$) and 20 mg (4.1, $P < 0.01$).

41. The pharmacological data provide a scientific basis for the greater efficacy of Nexium® in clinical trials. Further, as described above, Nexium® has demonstrated less inter-patient variability in AUC and gastric acid suppression than omeprazole, and thus may provide

[56] Lind et al. (2000), *supra* n.49.

[57] Lind et al. (2000), *supra* n.49.

doctors and patients with a more predictable response, which offers doctors additional reasons to prescribe Nexium® in addition to the clinical data described below.

(1) Nexium® Has Demonstrated More Effective Acid Suppression

42. As noted above, there is a correlation between the amount of acid entering the esophagus, the contact time of the refluxate with the esophageal lining, and the degree of esophagitis, providing a correlation between the severity of the abnormalities in regulation of the esophageal sphincter and the abnormalities seen at endoscopy.[58] Studies suggest that the severity of EE is associated with the extent and time that the esophageal tissue is exposed to refluxed stomach acid, with greater acid exposure resulting in more severe damage to esophageal tissue.[59]

43. The degree of acidity of the refluxate is measured in terms of pH. Stomach refluxate with pH less than 4 is associated with greater esophageal injury[60, 61, 62, 63], as well as with acid-related symptoms, like chronic heartburn, although symptoms may occur with refluxate that has a pH greater than 4 as well.[64, 65] The pH of gastric juice is generally between 1 and 2. Meals temporarily increase intra-gastric pH, but acid secretion then resumes and intra-

[58] Lundell LR, Dent J, Bennett JR, Blum AL, Armstrong D, Galmiche JP, Johnson F, Hongo M, Richter JE, Spechler SJ, Tytgat GN, Wallin L. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut. 1999 Aug;45(2):172-80.

[59] Holloway RH, Dent J, Narielvala F, et al. Relation between oesophageal acid exposure and healing of oesophagitis with omeprazole in patients with severe reflux oesophagitis. Gut 1996;38:649-54.

[60] Orlando RC. Why is the high grade inhibition of gastric acid secretion afforded by proton pump inhibitors often required for healing of reflux esophagitis? An epithelial perspective. Am J Gastroenterol 1996;91:1692-6.

[61] Berstad A. A modified hemoglobin substrate method for the estimation of pepsin in the gastric juice. Scand J Gastroenterol 1970;5:343-8.

[62] Fiorucci S, Santucci L, Chiucchiu S, et al. Gastric acidity and gastroesophageal reflux patterns in patients with esophagitis. Gastroenterology 1992;103:855-61.

[63] Roberts NB. Review article: human pepsins – their multiplicity, function and role in reflux disease Aliment Pharmacol Ther 2006;24(2):2-9.

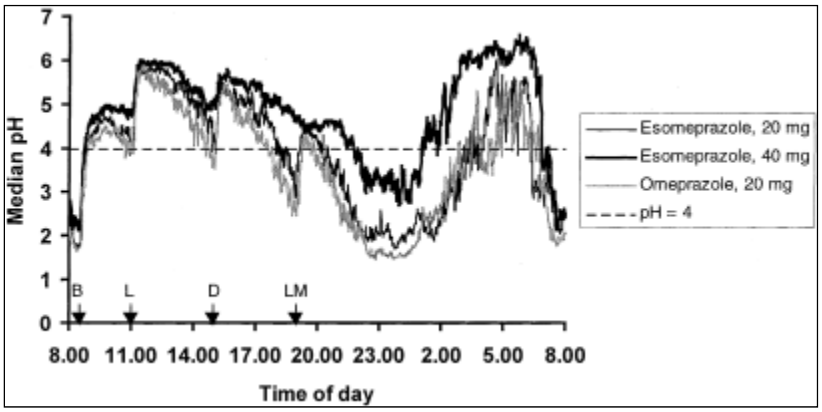
[64] Smith JL, Opekun AR, Larkai E, et al. Sensitivity of the esophageal mucosa to pH in gastroesophageal reflux disease. Gastroenterology 1989;96:683-9.

[65] Joelsson B, Johnsson, F. Heartburn—the acid test. Gut 1989;30:1523-5.

gastric pH falls again. All PPIs offer some measure of 24-hour acid control compared to no medication[66], and Nexium® is no exception. As pH is a logarithmic scale, small changes in pH correspond to large changes in acid secretion.

44. The figure below shows a trial comparing omeprazole and esomeprazole and demonstrates the differences in effects of these two PPIs on inhibiting gastric acid during a 24 hour period.[67]

Figure 2



45. Because proton pump inhibitors work by inhibiting stomach acid secretion, one way to assess their potency is by quantitatively evaluating their ability to inhibit acid secretion. Such studies are relevant to the comparison of PPIs, because GERD is an acid-related disease and there is evidence to suggest that greater acid control may effectively provide more reliable treatment of reflux disease and healing of erosive esophagitis.[68]

---

[66] Tutuian R, Katz P, Castell D. A PPI is a PPI is a PPI: lessons learned from longterm intragastric pH monitoring. Gastroenterology 2000;118 (suppl 2 part 1):A17 abstract 332.

[67] Lind T, Rydberg L, Kylebäck A, Jonsson A, Andersson T, Hasselgren G, Holmberg J, Röhss K Esomeprazole provides improved acid control vs. omeprazole In patients with symptoms of gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2000 Jul;14(7):861-7.

[68] Hunt RH. Importance of pH control in the management of GERD. Arch Intern Med. 1999 Apr 12;159(7):649-57. Review.

46. Acid inhibition studies are performed by placing an electrode in the stomach which measures gastric pH over a 24-hour period. In comparative studies, the same group of patients is treated with one proton pump inhibitor after another, with a wash-out period between treatments. Gastric pH is measured in each patient on each PPI. The conventional measure of acid inhibition is to determine the number of hours out of 24 that the gastric pH is maintained above 4, because the gastric juice becomes less injurious at a pH greater than 4.

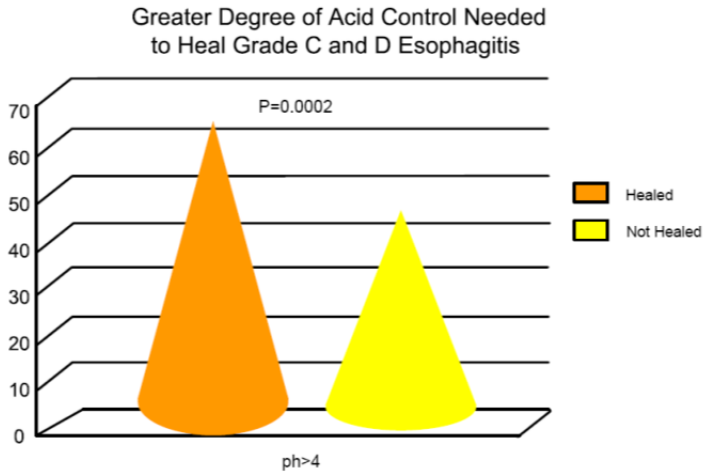
47. *Acid control over a 24-hour period* refers to a change in the pH curve of the stomach as shown in Figure 2 (above). It is important to recognize that *the time pH is controlled above 4* is a different but related concept. A pH of 4 is a threshold that has been developed based on the knowledge that pepsin, an enzyme secreted by the stomach, is activated at a pH that is less than 4. The material that refluxes into the esophagus is less damaging to the esophageal lining if the pH is greater than 4.[69]

48. The time that gastric acid is controlled above pH 4 may be related to healing in patients with erosive esophagitis, and published data suggest that failure to control gastric pH may play a role in treatment failure. For example, in a study of 103 patients with Los Angeles Classification Grade C and D esophagitis – the most severe grades of EE – patients in whom esophagitis healed with PPI therapy had gastric pH greater than 4 for 61% of the 24-hour period, while patients in whom esophagitis did not heal with PPI therapy had poorer control of gastric acid (gastric pH>4 for 42% of the 24 hour period; P=0.0002). Thus, in patients with Grade C

[69] *See* Roberts et al. (2006), *supra* n. 63..

and D disease, patients with healed esophagitis had longer periods with a pH > 4 than patients who failed to have healing of esophagitis, as reflected in Figure 3, below:[70]

Figure 3



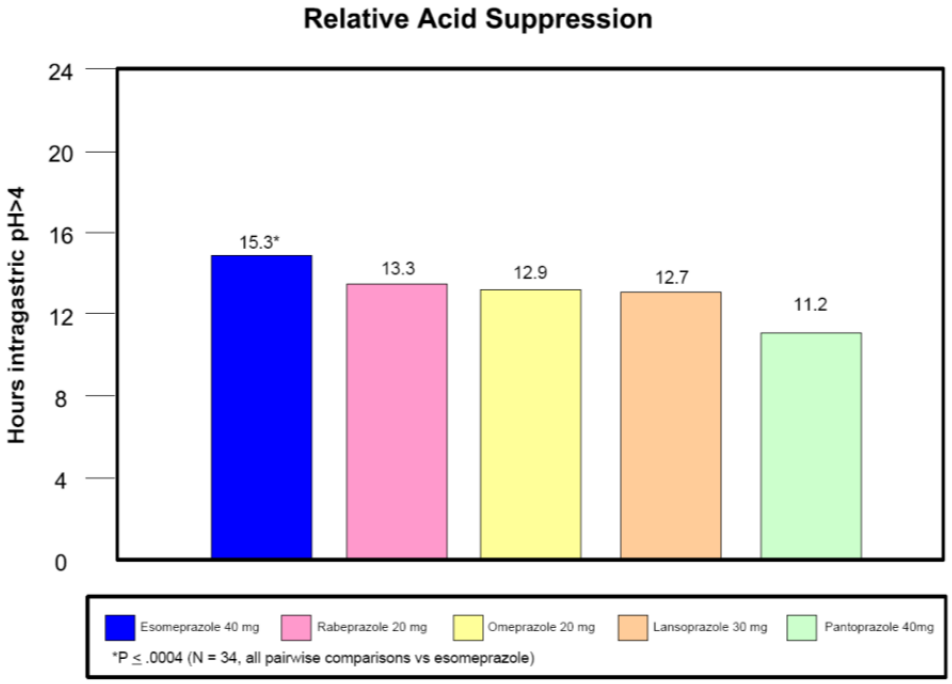
49. Given this understanding as to the role of acid suppression in treatment of acid reflux disease and the basic fact that all PPIs work by suppressing acid, a physician reasonably could consider the ability of the various PPIs to suppress acid in the physician's prescribing decisions. Doctors understand that acid suppression studies measure the pharmacodynamics, or action, of PPIs rather than their clinical effect on a particular disease or condition. This distinction is apparent on the labeling for Nexium® and all other PPIs, and it is a basic concept that doctors learn as part of their medical training. Acid suppression studies also provide doctors with useful information to help them care for patient subpopulations who may not be represented in randomized controlled clinical trials, for example: the very elderly, patients with other serious health care problems, and those who cannot undergo endoscopy. It is appropriate for doctors to

[70] Katz PO, Ginsberg GG, Hoyle PE, Sostek MB, Monyak JT, Silberg DG. Relationship between intragastric acid control and healing status in the treatment of moderate to severe erosive oesophagitis. Aliment Pharmacol Ther. 2007 Mar 1;25(5):617-28.

consider this relevant, objective measure of the effect of PPIs when considering the treatment options available to their patients.

50. Published studies have demonstrated that Nexium® provides more effective gastric acid suppression compared to other PPIs. In a randomized, open-label, comparative, 5-treatment, 5-way crossover study that compared the potency of 5 different PPIs, Nexium® (esomeprazole) provided a significant increase in the number of hours out of 24 that intragastric pH was greater than 4, compared with the other PPIs studied.[71, 72] The day 5 results of this study are reflected in the figure below:

Figure 4



[71] Miner P Jr, Katz PO, Chen Y, Sostek M. Gastric acid control with esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole: a five-way crossover study.Am J Gastroenterol. 2003;98:2616-2620.

[72] Miner P Jr, Katz PO, Chen Y, Sostek M. Reanalysis of intragastric pH results based on updated correction factors for Slimline and Zinetics 24 single-use pH catheters. Am J Gastroenterol. 2006;101:404-405. The data used in the study published in 2003 were re-analyzed in 2006, as were many other pH studies, when it was discovered that the Slimline catheter used in pH studies of this type had an error in its calibration curves. The correction did not alter the conclusions of the study or affect the results meaningfully.

51. Similar results were seen in a series of carefully performed studies that measured intra-gastric pH compared with all the currently available proton pump inhibitors in their approved doses. In healthy volunteers and in patients with reflux disease, esomeprazole 40 mg demonstrated better acid control than rabeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg and omeprazole 20 mg.[73, 74] Similar studies have also been performed for maintenance doses of esomeprazole comparing it to the approved maintenance doses of other proton pump inhibitors, once again demonstrating more effective suppression of gastric acid with esomeprazole.[75]

52. Nexium® 40 mg and omeprazole 40 mg also have been compared in a pH study of 114 patients with GERD, in which Nexium® 40 mg was shown to maintain gastric pH above 4 significantly longer than omeprazole 40 mg (both administered once a day for five days).[76] The mean percentage of the 24-hr. period with intragastric pH > 4 was significantly greater *(P < 0.001)* with esomeprazole 40 mg than with omeprazole 40 mg on days 1 (48.6% vs. 40.6%) and 5 (68.4% vs. 62.0%). Inter-patient variability was significantly less with esomeprazole than omeprazole.

53. The effect is also seen across ethnic groups. For example in another study of Hispanic individuals with GERD, Nexium® was more effective in controlling gastric acid

[73] Röhss K, Lind T, Wilder-Smith C. Esomeprazole 40 mg provides more effective intragastric acid control than lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg in patients with gastro-oesophageal reflux symptoms. Eur J Clin Pharmacol. 2004 Oct;60(8):531-9

[74] Wilder-Smith CH, Röhss K, Nilsson-Pieschl C, Junghard O, Nyman L.Esomeprazole 40 mg provides improved intragastric acid control as compared with lansoprazole 30 mg and rabeprazole 20 mg in healthy volunteers. Digestion. 2003;68(4):184-8. Epub 2003 Dec 19

[75] Röhss K, Wilder-Smith C, Nauclér E, Jansson L. Esomeprazole 20mg provides more effective intragastric Acid control than maintenance-dose rabeprazole, lansoprazole or pantoprazole in healthy volunteers.Clin Drug Investig. 2004;24(1):1-7

[76] Röhss K, Hasselgren G, Hedenström H. Effect of esomeprazole 40 mg vs omeprazole 40 mg on 24-hour intragastric pH in patients with symptoms of gastroesophageal reflux disease. Dig Dis Sci. 2002 May;47(5):954-8.

compared to lansoprazole and pantoprazole. This study was important because it measured acid in the lower part of the stomach and also measured acidity in the acid pocket close to the gastro-esophageal junction where much of the acid-related injury occurs. [77]

54. Thus, doctors reasonably may consider this acid suppression data demonstrating Nexium®'s better acid control compared to all other PPIs a reason to prescribe Nexium® instead of omeprazole or any other PPI, because acid suppression is a key aspect of the treatment of GERD and its complications.

(2) Nexium® Has Demonstrated Higher Rates of Healing Erosive Esophagitis

55. Regulatory studies concerning proton pump inhibitors and H_2RAs have focused on healing of erosive esophagitis as a therapeutic end-point of clinical trials, and healing of erosive esophagitis has been one of the primary endpoints for many trials involving all of the available PPIs. This end-point is used in clinical trials because: (a) the presence of erosions confirms the presence of reflux disease; (b) healing of erosions is an objective end-point that can be measured by different endoscopists with good accuracy; and (c) healing of esophagitis prevents serious complications, making it a valid measure of treatment efficacy.

56. Nexium® has demonstrated higher rates of healing erosive esophagitis in studies compared to omeprazole. In four studies that are reported in the FDA-approved Nexium® labeling, healing of erosive esophagitis was evaluated in double-blind, randomized, controlled trials that compared two doses of Nexium® (esomeprazole) with the FDA-approved 20 mg dose

[77] Morgan D, Pandolfino J, Katz PO, Goldstein JL, Barker PN, Illueca M. Clinical trial: gastric acid suppression in Hispanic adults with symptomatic gastro-oesophageal reflux disease - comparator study of esomeprazole, lansoprazole and pantoprazole. Aliment Pharmacol Ther. 2010 Jul;32(2):200-8.

of Prilosec (omeprazole) for healing erosive esophagitis.[78, 79, 80, 81] In all four studies, patients with erosive esophagitis were randomized to treatment with esomeprazole or omeprazole. Healing was assessed endoscopically, and the principal end-point of the trial was to determine the proportion of patients who had complete healing of esophagitis at 8 weeks; week 4 healing data and symptom data were secondary end-points.

57. In two of these studies, esomeprazole 40 mg provided statistically significant higher rates of healing EE than omeprazole 20 mg.[82] In a third study, Nexium® 40 mg showed numerically higher healing rates, but the results did not reach statistical significance.[83] These results can be displayed as follows:

[78] Richter JE, Kahrilas PJ, Johanson J, Maton P, Breiter JR, Hwang C, Marino V, Hamelin B, Levine JG; Esomeprazole Study Investigators. Efficacy and safety of esomeprazole compared with omeprazole in GERD patients with erosive esophagitis: a randomized controlled trial. Am J Gastroenterol. 2001;96:656-665.

[79] Kahrilas PJ, Falk GW, Johnson DA, Schmitt C, Collins DW, Whipple J, D'Amico D, Hamelin B, Joelsson B.Esomeprazole improves healing and symptom resolution as compared with omeprazole in reflux oesophagitis patients: a randomized controlled trial. The Esomeprazole Study Investigators. Aliment Pharmacol Ther. 2000 Oct;14(10):1249-58.

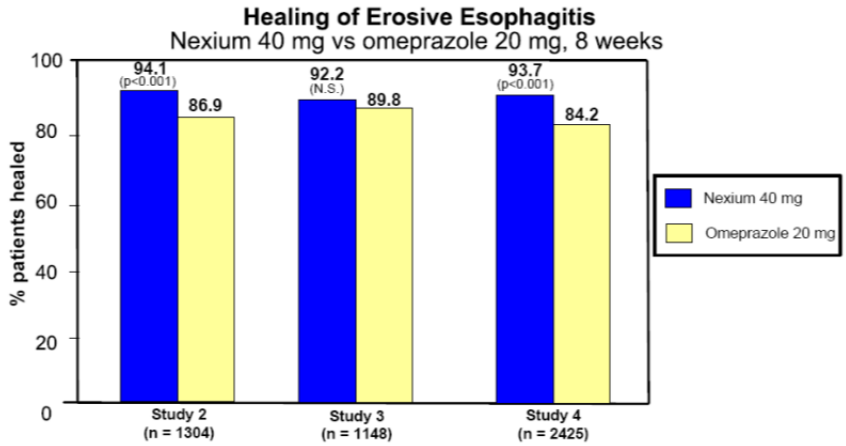
[80] Schmitt C, Lightdale CJ, Hwang C, Hamelin B. A multicenter, randomized, double-blind, 8-week comparative trial of standard doses of esomeprazole (40 mg) and omeprazole (20 mg) for the treatment of erosive esophagitis.Dig Dis Sci. 2006;51:844-850

[81] Lightdale CJ, Schmitt C, Hwang C, Hamelin B. A multicenter, randomized, double-blind, 8-week comparative trial of low-dose esomeprazole (20 mg) and standard-dose omeprazole (20 mg) in patients with erosive esophagitis. Dig Dis Sci. 2006 May;51(5):852-7. Epub 2006 Jun 14.

[82] *See* Richter, et al. (2001), *supra* n. 78; Kahrilas, et al. (2000), *supra* n. 79.

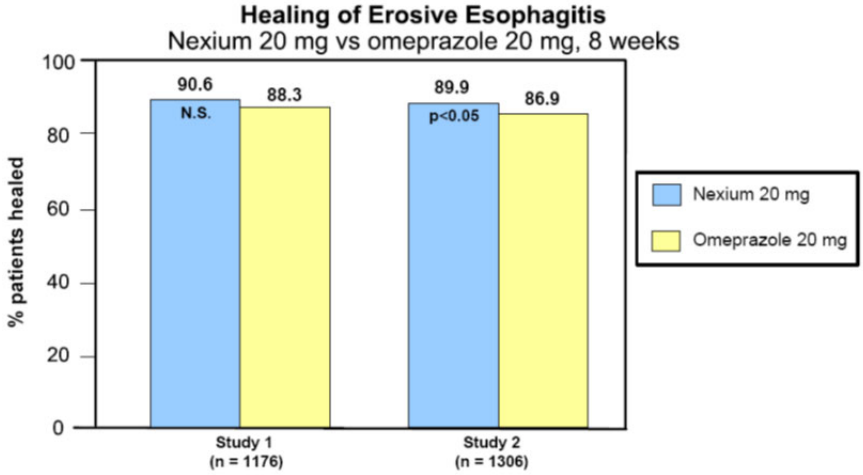
[83] *See* Schmitt, et al. (2006), *supra* n. 80.

Figure 5[84]



58. Nexium® 20 mg also showed numerically higher 8-week healing rates than Prilosec 20 mg in two studies, and the results were statistically significant in one of the two studies.[85] The results can be displayed as follows:

Figure 6



[84]The Study number in the chart refers to the corresponding number for the study used on the Nexium labeling, as reflected in Figure 7, below. Thus, Study 1 on the labeling is the study by Lightdale, et al., *supra* n. 81; Study 2 on the labeling is the study by Kahrilas, et al., *supra* n. 79; Study 3 on the labeling is the study by Schmitt, et al., *supra* n. 80; Study 4 on the labeling is the study by Richter, et al., *supra* n. 78. In his declaration, Dr. Abramson also refers to these studies as 172, 173, 174, and 222. Study 1 on the labeling is Study 173; Study 2 on the labeling is Study 172; Study 3 on the labeling is Study 174; and Study 4 on the labeling is Study 222.

[85] *See* Kahrilas, et al. (2000), *supra* n. 79; Lightdale, et al. (2006), *supra* n. 81.

59. The results of these four trials are shown in tabular form in the labeling, or package insert, for Nexium®, as reproduced below:

Figure 7

Erosive Esophagitis Healing Rate (Life-Table Analysis)

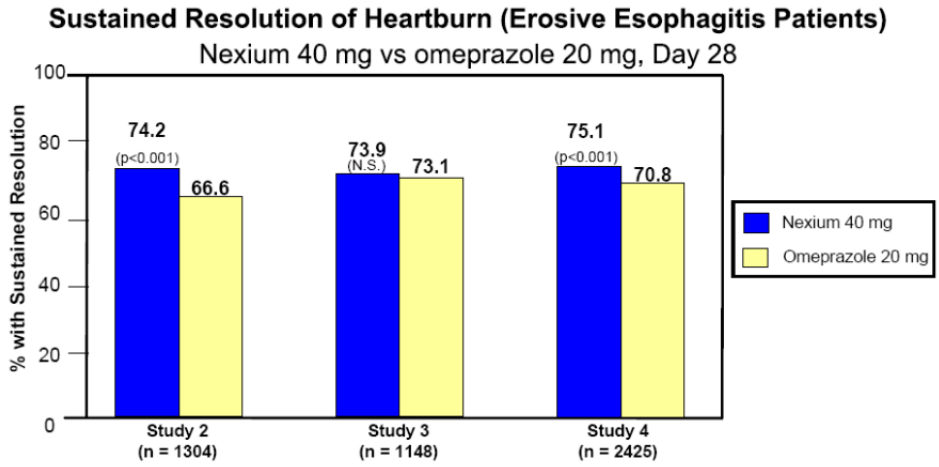
Study	No. of Patients	Treatment Groups	Week 4	Week 8	Significance Level *
1	588	NEXIUM 20 mg	68.7%	90.6%	N.S.
	588	Omeprazole 20 mg	69.5%	88.3%	
2	654	NEXIUM 40 mg	75.9%	94.1%	$p < 0.001$
	656	NEXIUM 20 mg	70.5%	89.9%	$p < 0.05$
	650	Omeprazole 20 mg	64.7%	86.9%	
3	576	NEXIUM 40 mg	71.5%	92.2%	N.S.
	572	Omeprazole 20 mg	68.6%	89.8%	
4	1216	NEXIUM 40 mg	81.7%	93.7%	$p < 0.001$
	1209	Omeprazole 20 mg	68.7%	84.2%	

*log-rank test vs omeprazole 20 mg
N.S. = not significant ($p > 0.05$).

60. In the same four trials, resolution of heartburn was assessed as well. The controlled trials for Nexium® introduced a new and more rigorous end-point into clinical trials for GERD. This end-point was complete resolution of symptoms (rather than improvement of symptoms) lasting for 7 consecutive days. In two studies, Nexium® 40 mg provided statistically significantly more rapid and complete heartburn control in EE patients than omeprazole 20 mg.[86] The results of the comparisons of Nexium® 40 mg and omeprazole 20 mg are displayed below:

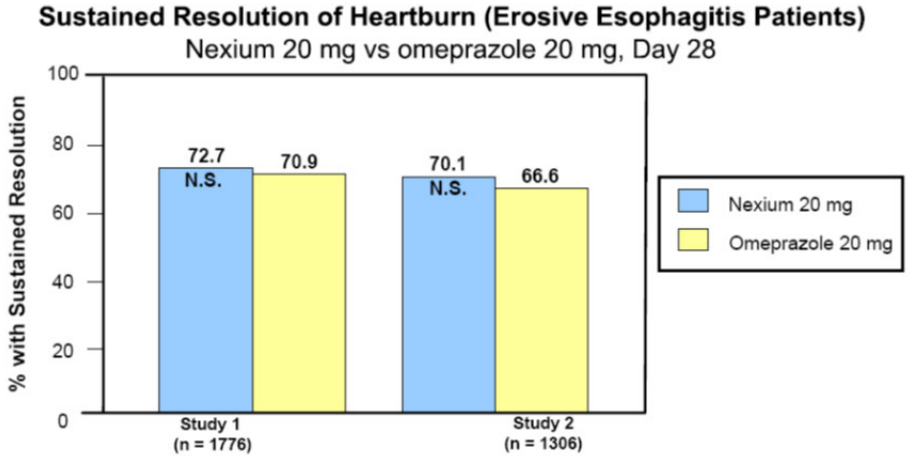
[86] *See* Richter et al. (2001), *supra* n. 78; Kahrilas et al. (2000), *supra* n. 79.

Figure 8



61. The results of the comparisons of Nexium® 20 mg and omeprazole 20 mg, which were not statistically significant, are displayed below:

Figure 9



62. A summary of the results of symptom resolution also was provided on the FDA-approved Nexium® labeling, as reproduced below:

Figure 10

Sustained Resolution‡ of Heartburn (Erosive Esophagitis Patients)

			Cumulative Percent# with Sustained Resolution		
Study	No. of Patients	Treatment Groups	Day 14	Day 28	Significance Level *
1	573	NEXIUM 20 mg	64.3%	72.7%	N.S.
	555	Omeprazole 20 mg	64.1%	70.9%	
2	621	NEXIUM 40 mg	64.8%	74.2%	p <0.001
	620	NEXIUM 20 mg	62.9%	70.1%	N.S.
	626	Omeprazole 20 mg	56.5%	66.6%	
3	568	NEXIUM 40 mg	65.4%	73.9%	N.S.
	551	Omeprazole 20 mg	65.5%	73.1%	
4	1187	NEXIUM 40 mg	67.6%	75.1%	p <0.001
	1188	Omeprazole 20 mg	62.5%	70.8%	

‡Defined as 7 consecutive days with no heartburn reported in daily patient diary.
#Defined as the cumulative proportion of patients who have reached the start of sustained resolution
*log-rank test vs omeprazole 20 mg
N.S. = not significant (p > 0.05).

63. Further, as stated on the labeling, in these four studies of EE patients, "the range of median days to the start of sustained resolution (defined as 7 consecutive days with no heartburn) was 5 days for Nexium® 40 mg, 7-8 days for Nexium® 20 mg, and 7-9 days for omeprazole 20 mg."

64. Other randomized controlled trials have compared Nexium® 40 mg to other agents in the PPI class for healing of EE across all grades.[87, 88, 89, 90, 91] All were randomized

[87] *See* Richter et al. (2001), *supra* n. 78.

[88] *See* Kahrilas et al. (2000), *supra* n. 79.

[89] *See* Schmitt et al. (2006), *supra* n. 80.

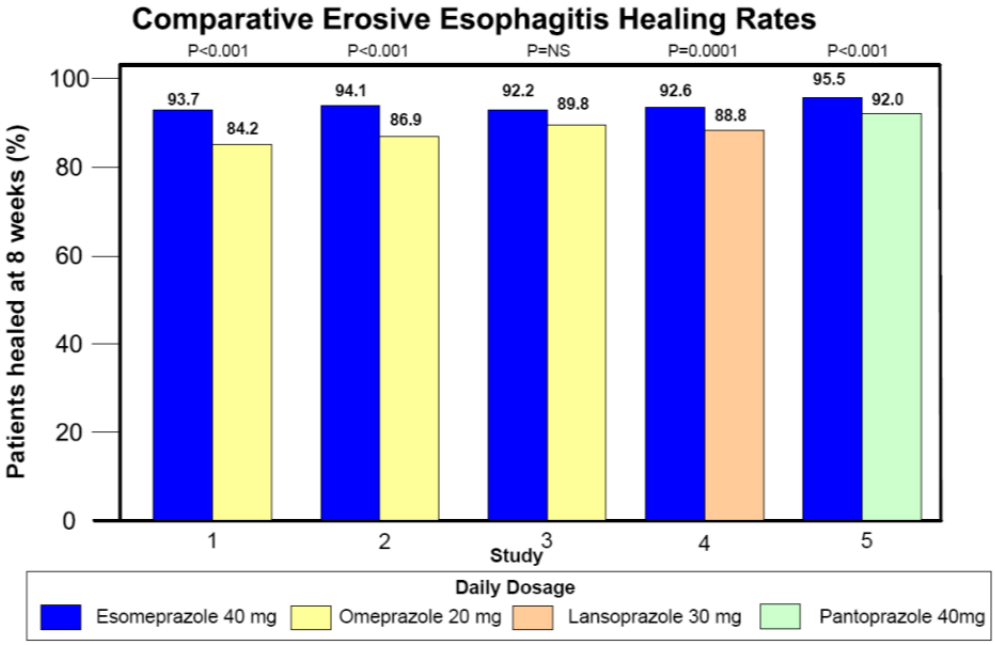
[90] Castell DO, Kahrilas PJ, Richter JE, Vakil NB, Johnson DA, Zuckerman S, Skammer W, Levine JG. Esomeprazole (40 mg) compared with lansoprazole (30 mg) in the treatment of erosive esophagitis. Am J Gastroenterol. 2002;97:575-583.

[91] Labenz J, Armstrong D, Lauritsen K, Katelaris P, Schmidt S, Schütze K, Wallner G, Juergens H, Preiksaitis H, Keeling N, Nauclér E, Eklund S; Expo Study Investigators. A randomized comparative study of esomeprazole

(Footnote continued)

controlled trials with healing of erosive esophagitis as the primary end-point. The results of these trials are summarized graphically below:

Figure 11



1. Richter JE, et al. Am J Gastroenterol. 2001;96:656-665. 2. Kahrilas PJ, et al. Aliment Pharmacol Ther. 2000;14:1249-1258. 3. Schmitt C, et al. Dig Dis Sci. 2006;51:844-850. 4. Castell DO, et al. Am J Gastroenterol. 2002;97:575-583. 5. Labenz J, et al. Aliment Pharmacol Ther. 2005;21:739-746.

65. These data thus demonstrate Nexium®'s higher rates of healing in erosive esophagitis, and its demonstrated symptom resolution in EE patients. A doctor might reasonably consider these data a reason to prescribe Nexium® over omeprazole or other PPIs.

(3) Nexium® Has Demonstrated Greater Efficacy in Healing Severe Esophagitis

66. The ability of a PPI to heal severe esophagitis (Los Angeles Grade C and D disease) is important because patients with more severe EE tend to have greater esophageal acid exposure and tend to be more difficult to heal. They are also at the highest risk for serious complications, such as major bleeding, stricture, and ulceration. Moreover, patients with GERD

40 mg versus pantoprazole 40 mg for healing erosive oesophagitis: the EXPO study. Aliment Pharmacol Ther. 2005 Mar 15;21(6):739-46.

frequently are treated without performing an endoscopy. However, when an endoscopy is performed, the endoscopy reveals esophagitis in some patients,[92] which for some patients is severe (Grade C or D). Physicians thus may elect to prescribe a PPI with proven ability in comparative clinical trials to more effectively heal the most severe erosions.[93]

67. Furthermore, the results of a drug that is more effective for more severe disease may not be as apparent in trials where large proportions of patients with mild disease are enrolled. In contrast, the advantages of a drug may be more readily apparent in patients with more advanced disease. Therefore, it is reasonable to evaluate improvements in treatment response by evaluating a group of patients with more severe disease.

68. The greater healing ability of Nexium® is most apparent in more severe esophagitis. For example, Nexium® was compared to lansoprazole in patients with Los Angeles Grades C and D disease in one trial in which healing was the primary objective of the trial.[94] In this trial, healing rates at week 8 with Nexium® 40 mg were 82.4% compared to 77.5% with lansoprazole 30 mg (p=0.007, comparison of the time-to-healing using a log rank test). A significantly greater proportion of patients had resolution of their symptoms at week 4 with Nexium® (72% versus 63.6%, p=0.005). In addition, post hoc analyses of six other studies, including studies against omeprazole, showed a statistically significant difference favoring Nexium® in the healing of Grades C and D esophagitis in 5 of the 6 studies. [95, 96, 97, 98, 99, 100, 101]

[92] Ruigómez A, Rodríguez LA, Wallander MA, Johansson S, Dent J. Endoscopic findings in a cohort of newly diagnosed gastroesophageal reflux disease patients registered in a UK primary care database. Dis Esophagus. 2007;20(6):504-8.

[93] Gralnek IM, Dulai GS, Fennerty MB, Spiegel BM. Esomeprazole versus other proton pump inhibitors in erosive esophagitis: a meta-analysis of randomized clinical trials. Clin Gastroenterol Hepatol. 2006 Dec;4(12):1452-8.

[94] Fennerty MB, Johanson JF, Hwang C, Sostek M. Efficacy of esomeprazole 40 mg vs. lansoprazole 30 mg for healing moderate to severe erosive oesophagitis. Aliment Pharmacol Ther. 2005 Feb 15;21(4):455-63.

[95] Richter et al. (2001), *supra* n. 78.

Furthermore, as described below, a meta-analysis of randomized controlled trials confirms that Nexium® provides higher healing rates in Grade C and D disease. Doctors might reasonably consider this data concerning Nexium®'s greater efficacy in healing severe esophagitis a reason to prescribe Nexium® over omeprazole and other PPIs.

(4) Efficacy of Nexium® 40 mg Is Confirmed in Meta-Analysis of Clinical Trials

69. The efficacy of Nexium® versus other PPIs has been confirmed in a meta-analysis of clinical trials. Meta-analysis is a statistical procedure that integrates the results of several independent studies considered to be "combinable."[102, 103] Well-conducted meta-analyses allow a more objective appraisal of the evidence than traditional narrative reviews, provide a more precise estimate of a treatment effect, and may explain heterogeneity between the results of individual studies.[104] A well-conducted systematic review precedes a quantitative meta-analysis and utilizes measures of study quality that are used to select studies for inclusion into the quantitative aspect of the study.

70. The relative benefit of an active treatment over a control is usually expressed as the relative risk, the relative risk reduction, or the odds ratio. For clinical decision making, however, it is clinically meaningful to use a measure called "number needed to treat." This

[96] Kahrilas et al. (2000), *supra* n. 79.

[97] Schmitt et al. (2006), *supra* n. 80.

[98] Lightdale et al. (2006), *supra* n. 81.

[99] Castell et al. (2002), *supra* n. 90.

[100] Labenz et al. (2005), *supra* n. 91.

[101] Fennerty, et al. (2005), *supra* n. 94.

[102] Egger M, Davey Smith G. Meta-analysis: potentials and promise. BMJ 1997;315:1371-4

[103] Egger M, Smith GD, Phillips A. Meta-analysis: Principles and procedures BMJ 1997;315:1533-1537

[104] *See* Egger, et al., *supra* n. 102, 103.

measure is calculated on the inverse of the absolute risk reduction. It has the advantage that it conveys both statistical and clinical significance to the doctor.[105] In the case of proton pump inhibitors, the number needed to treat is the number of patients you need to treat to create one additional better outcome (i.e., healing of erosive esophagitis).

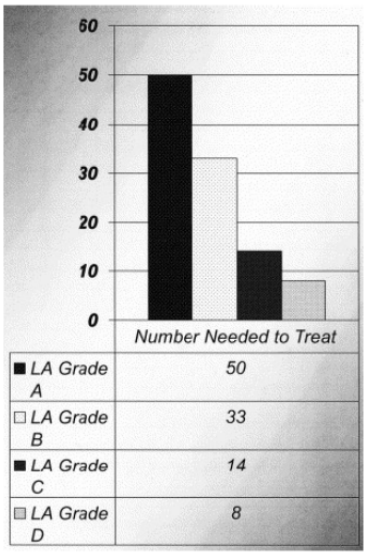
71. A meta-analysis was performed to calculate the pooled effect of esomeprazole on healing rates, symptom relief, and adverse events versus competing PPIs in patients with erosive esophagitis.[106] The authors identified 10 studies that evaluated 15,316 patients. These 10 studies included 8 peer-reviewed, full-text manuscripts, 1 published abstract, and 1 manufacturer package insert. At 8 weeks after initiation of therapy, there was a 5% (Relative risk= 1.05; 95% confidence interval, 1.02–1.08) relative increase in the probability of healing of erosive esophagitis with esomeprazole compared to all other PPIs, yielding an absolute risk reduction of 4% and number needed to treat of 25 (number of patients needed to be treated with esomeprazole to get one additional responder compared to other proton pump inhibitors).

72. If the results are broken down by grade of esophagitis, the number of patients that need to be treated with esomeprazole 40 mg to get an additional responder compared to other proton pump inhibitors were: Los Angeles Grade A=50 patients, Los Angeles Grade B=33 patients, Los Angeles Grade C=14 patients and Grade D=8 patients, as reflected in the following figure reproduced from the publication:

[105] Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. BMJ 1995; 310: 452-454.

[106] Gralnek IM, Dulai GS, Fennerty MB, Spiegel BM.Esomeprazole versus other proton pump inhibitors in erosive esophagitis: a meta-analysis of randomized clinical trials. Clin Gastroenterol Hepatol. 2006 Dec;4(12):1452-8.

Figure 12



73. This meta-analysis confirms the superiority of Nexium® in healing the most severe disease. Based on this meta-analysis, a reasonable gastroenterologist or other physician may therefore conclude that Nexium® 40 mg offers a significant advantage to patients, especially those with more severe disease.

(5) Nexium® Is Effective in Maintenance of Healing of Erosive Esophagitis

74. Erosive esophagitis is chronic in the majority of cases; GERD is a chronic disorder and most patients who cease treatment are likely to relapse. Therefore, long-term studies of the maintenance of healing of erosive esophagitis are an important consideration in GERD therapy.

75. Two randomized controlled trials have demonstrated that Nexium® is effective versus placebo in maintaining the healing of EE. These trials evaluated patients who had been treated with either esomeprazole or omeprazole and had complete healing of erosive

esophagitis.[107, 108] After healing of erosive esophagitis, patients were randomized to placebo, esomeprazole 10 mg, esomeprazole 20 mg, or esomeprazole 40 mg. The primary endpoint was endoscopic relapse of mucosal breaks and/or study discontinuation due to symptomatic relapse. Both studies demonstrated that esomeprazole 20 mg and 40 mg are effective in maintaining healing of EE. Like the results of the trials for healing EE, the results of these studies are shown on the FDA-approved Nexium® package insert, and the FDA approved 20 mg Nexium® as the recommended dose for maintenance of healing of EE.

76. In addition, two randomized controlled trials compared Nexium 20 mg to lansoprazole 15 mg (both FDA-approved maintenance doses of the medication) for maintenance of healing of erosive esophagitis. In the first trial, patients treated with Nexium® 20 mg once daily consistently maintained statistically significantly higher remission rates than those treated with lansoprazole 15 mg once daily, regardless of baseline disease severity (83% vs. 74%, $p<0.0001$).[109] Similarly, in the second trial, patients receiving Nexium® 20 mg evidenced statistically significantly better maintained healing compared with lansoprazole 15 mg. (endoscopic and symptomatic remission, 84.8% vs. 75.9%, $p=0.0007$).[110]

---

[107] Johnson DA, Benjamin SB, Vakil NB, Goldstein JL, Lamet M, Whipple J, Damico D, Hamelin B. Esomeprazole once daily for 6 months is effective therapy for maintaining healed erosive esophagitis and for controlling gastroesophageal reflux disease symptoms: a randomized, double-blind, placebo-controlled study of efficacy and safety. Am J Gastroenterol. 2001 Jan;96(1):27-34. Erratum in: Am J Gastroenterol 2001 Mar;96(3):942.

[108] Vakil NB, Shaker R, Johnson DA, Kovacs T, Baerg RD, Hwang C, D'Amico D, Hamelin B. The new proton pump inhibitor esomeprazole is effective as a maintenance therapy in GERD patients with healed erosive oesophagitis: a 6-month, randomized, double-blind, placebo-controlled study of efficacy and safety. Aliment Pharmacol Ther. 2001 Jul;15(7):927-35.

[109] Lauritsen K, Devière J, Bigard MA, Bayerdörffer E, Mózsik G, Murray F, Kristjánsdóttir S, Savarino V, Vetvik K, De Freitas D, Orive V, Rodrigo L, Fried M, Morris J, Schneider H, Eklund S, Larkö A; Metropole study results. Esomeprazole 20 mg and lansoprazole 15 mg in maintaining healed reflux oesophagitis: Metropole study results. Aliment Pharmacol Ther. 2003 Feb;17(3):333-41.

[110] Devault KR, Johanson JF, Johnson DA, Liu S, Sostek MB. Maintenance of healed erosive esophagitis: a randomized six-month comparison of esomeprazole twenty milligrams with lansoprazole fifteen milligrams. Clin Gastroenterol Hepatol. 2006 Jul;4(7):852-9. Epub 2006 May 6.

(6) Nexium® Works When Other Therapies Have Failed

77. Pragmatic studies are studies that are performed in real life conditions and provide an important glimpse into how drugs work in real life, outside the carefully controlled conditions that exist in a randomized controlled trial.

78. Many patients on proton pump inhibitors other than Nexium® are unhappy with their therapy and continue to experience symptoms that affect their quality of life. In many instances, when they are switched to Nexium® treatment, their satisfaction with treatment increases significantly. This is something I have observed in my own practice. It also has been demonstrated in published studies.

79. For example, in a large Dutch study of 4929 patients, only 21.9% of patients reported that they were satisfied with their PPI treatment at consultation (i.e. prior to switching to esomeprazole). Following switching to esomeprazole therapy, 88.0% of patients reported that they were satisfied with therapy and only 26.9% of patients were still experiencing symptoms (vs. 84.0% at consultation); 71.3% reported that they were more satisfied with esomeprazole than with their previous PPI, most frequently because they had fewer or no symptoms. Among patients who had been using an additional therapy to control GERD symptoms, 62.0% were no longer using any such medication. Of the 1069 patients who had been satisfied with their previous PPI therapy, 39.4% were even more satisfied with esomeprazole.[111]

80. Another study from the United Kingdom found similar results. Patients who did not have adequate control of their symptoms on other proton pump inhibitors improved

[111] Hoogendoorn RJ, Groeneveld L, Kwee JA, Patient Satisfaction with Switching to Esomeprazole from Existing Proton Pump Inhibitor Therapy for Gastro-Oesophageal Reflux Disease Clin Drug Investig 2009; 29 (12): 803-810.

significantly when they were switched to Nexium®.[112] Patients with GERD in a general practice setting who were dissatisfied with their current proton pump inhibitor therapy were offered entry into a trial where they were switched to Nexium® 40 mg/day. The mean frequency of heartburn was reduced by 78% from 4.4 days a week to 1 day a week at the end of the 8-week treatment period ($p < 0.0001$). Other GERD symptoms were also significantly reduced following of treatment with esomeprazole (all $p < 0.0001$).

81. In a practice setting in Canada, patients who were still symptomatic on other proton pump inhibitors had a significant improvement in quality adjusted months when switched to esomeprazole, and the treatment was cost-effective. The majority of patients were receiving antisecretory therapy other than esomeprazole (rabeprazole, 24.7 % ; pantoprazole, 20.5 % ; lansoprazole, 12.9 % ; omeprazole, 12.5 % ; or ranitidine, 16.8 %). After 4-week follow-up, there was a statistically significant benefit of esomeprazole vs. usual care in terms of participants symptom rating, with 563 / 973 (58 %) recording their symptoms as none or minimal over the previous 2 days compared with 170 / 591 (29 %) in the control group ($P < 0.0001$, intention to treat (ITT) analysis). There was also a statistically significant improvement in symptom score at 4 weeks in the esomeprazole arm compared with the control arm (difference in GOS score = − 0.9; 95 % confidence interval. This study in a real-life setting demonstrates that Nexium® is superior to other agents in routine practice settings and the improved outcomes are cost-effective.[113]

---

[112] R. Jones, T. Patrikios, The effectiveness of esomeprazole 40 mg in patients with persistent symptoms of gastro-oesophageal reflux disease following treatment with a full dose proton pump inhibitor Int J Clin Pract, December 2008, 62, 12, 1844–1850.

[113] Moayyedi P, David Armstrong, Hunt R, Lei Y, Bukoski White R. The Gain in Quality-Adjusted Life Months by Switching to Esomeprazole in Those With Continued Reflux Symptoms in Primary Care: EncomPASS — A Cluster-Randomized Trial. Am J Gastroenterol 2010; 105:2341–2346.

82. A study of 1,564 patients recruited from primary care centers across Canada has also demonstrated a statistically significant benefit *versus* control when patients were switched to Nexium® from their existing PPI therapies (including rabeprazole, pantoprazole, lansoprazole and omeprazole).[114] Additional data from this study show that switching to esomeprazole improved the sleep disturbance caused by night time reflux in these patients.[115]

83. Nexium® is the only PPI that has been shown to be superior to surgery for reflux disease.[116]

(7) Nexium® Is More Effective in Inhibiting H Pylori at Once-Daily Dosing

84. H pylori is an organism that causes peptic ulcer disease and gastric cancer. Nexium® is more effective in inhibiting H pylori than omeprazole. In a study of isolates of H pylori, Gatta et al. reported that the MIC50 and MIC90 (measures of how the drug inhibits the growth of H pylori) of esomeprazole were 16 and 32 mg/L.[117] In contrast the MIC of omeprazole was twice as high at 32 and 64 mg/L, reflecting less inhibition of growth of H pylori with omeprazole. Overall, 63.5% of isolates showed the same susceptibility to both drugs; 17 isolates were two- to 64-fold more susceptible to esomeprazole and two isolates were two-fold more susceptible to omeprazole. The authors concluded that the increased antimicrobial activity in vitro of esomeprazole against H pylori could contribute to improving the outcome of the

[114] Moayyedi *et al*, "The gain in quality-adjusted life months by switching to esomeprazole in those with continued reflux symptoms in primary care EncomPASS - a cluster-randomised-trial", *American Journal of Gastroenterology*, (2010), 105, 2341-2346.

[115] Moayyedi et al, "The impact of intensifying acid suppression on sleep disturbance related to gastro-oesophageal reflux disease in primary care" *Aliment Pharmacol Ther*, (2013), 37(7):730-7.

[116] Galmiche JP et al, "Laparoscopic antireflux surgery vs esomeprazole treatment for chronic GERD: the LOTUS randomized clinical trial", *JAMA*, (2011), 305(19), 1969-77.

[117] Gatta L, Perna F, Figura N, Ricci C, Holton J, D'Anna L, Miglioli M, Vaira D. Antimicrobial activity of esomeprazole versus omeprazole against Helicobacter pylori. J Antimicrob Chemother. 2003 Feb;51(2):439-42.

eradication treatment of such an infection. This is borne out in clinical studies, as Nexium® is the only proton pump inhibitor to be approved in a triple therapy regimen as a once-a-day treatment on 10 days dosing. All other PPIs must be given twice a day, or for a longer period of time, to achieve efficacy.[118] This is reflected in the approvals for proton pump inhibitors for H pylori treatment with triple therapy. Omeprazole, pantoprazole, lansoprazole and rabeprazole are all approved by the FDA for treatment of H pylori infection in combination with amoxicillin and clarithromycin but all need to be administered twice a day. In contrast, esomeprazole is approved in the same treatment regimen using the same doses of amoxicillin and clarithromycin, with esomeprazole administered only once a day.

85. In an analysis of 3 randomized, controlled trials of therapy for H pylori, esomeprazole administered once a day achieved eradication rates that were virtually identical to that of other twice-daily proton pump inhibitor-based triple therapies. [119] In my opinion, this is another demonstration of the superiority of this drug.

III. SUMMARY OF CLINICAL ADVANTAGES OF NEXIUM®

86. Nexium® provides more predictable treatment response and has demonstrated advantages over omeprazole and other PPIs that support the use of Nexium® over omeprazole or other PPIs for appropriate patients in the treatment of acid reflux disease.

87. Clinical studies demonstrate advantages with Nexium® over omeprazole and other PPIs and that Nexium® offers a superior treatment option for appropriate patients.

---

[118] Anagnostopoulos GK, Tsiakos S, Margantinis G, Kostopoulos P, Arvanitidis D. Esomeprazole versus omeprazole for the eradication of Helicobacter pylori infection: results of a randomized controlled study.J Clin Gastroenterol. 2004 Jul;38(6):503-6.

[119] Laine, L., Fennerty, M. B., Osato, M., Sugg, J., Suchower, L., Probst, P. et al. Esomeprazole-based Helicobacter pylori eradication therapy and the effect of antibiotic resistance: results of three US multicenter, double-blind trials. American Journal of Gastroenterology 2000; 5, 3393-8.

- ***Better acid control in the stomach***

  Medical treatment of acid reflux disease focuses on suppression of gastric acid, and published studies have demonstrated that Nexium® provides more prolonged gastric acid suppression compared to omeprazole and other PPIs.

- ***More predictable bioavailability and less inter-patient variability***

  Nexium® has demonstrated more predictable efficacy in healing of all grades of erosive esophagitis ("EE") – damage to the lining of the esophagus caused by reflux of stomach contents into the esophagus – compared with omeprazole. Nexium also has demonstrated less inter-patient variability in AUC (bioavailability) and gastric acid suppression than omeprazole and thus may provide doctors and patients with a more predictable response.

- ***Higher rates of healing erosive esophagitis***

  Nexium® has demonstrated higher rates of healing EE and faster time to start of sustained symptom resolution in EE patients when compared to the standard 20 mg dose of omeprazole approved by FDA for treatment of EE. Nexium® also has demonstrated higher healing rates in studies against Prevacid® (lansoprazole) and Protonix® (pantoprazole), and it has been shown to be more effective than other PPIs in healing the most severe grades of EE.

- ***Better efficacy in maintenance of healing compared to lansoprazole***

  In addition, Nexium® has been demonstrated to be safe and effective in maintaining the healing of EE, and more effective than lansoprazole in its approved doses in maintaining the healing of EE, an important criterion as GERD is a chronic disease.

- ***Better symptom control***

  Nexium® address the needs of patients who are still symptomatic on omeprazole and other PPIs, further demonstrating its superiority. Patients are concerned with the control of their symptoms, but many patients continue to report persistent reflux symptoms even on PPI therapy. Peer-reviewed studies have demonstrated that patients with such persistent symptoms on other proton pump inhibitors, including but not limited to omeprazole, improve after being switched to Nexium®. Moreover, in a cost-constrained environment, the use of Nexium® has been shown to be cost-effective for patients dissatisfied with the symptom relief accorded by the other proton pump inhibitors they were taking.

- ***Better activity against H pylori***

  Nexium® has better anti-bacterial activity against *H. pylori*. It is the only PPI approved for eradication of *H. pylori* in a single daily dose in combination with antibiotics (clarithromycin and amoxicillin); all other proton pump inhibitors approved for *H. pylori* eradication need to be administered twice a day. Proton pump inhibitors are a major component of the cost of *H. pylori* treatment, and reducing the dose by 50% may offer significant cost-savings.

88. Together, these data show that Nexium® (esomeprazole magnesium) has a unique place in the management of patients with GERD particularly the management of difficult patients and those who have failed other forms of therapy.

IV. INTRODUCTION OF A NEW BRANDED PPI

89. During my career, I have witnessed the launch of multiple proton pump inhibitors (Prevacid®, Aciphex®, Protonix®, Nexium®, Zegerid®). I have witnessed these launches as a practicing gastroenterologist and as an expert in reflux disease. I have participated in educational activities related to each of these agents. I served on advisory boards for Prevacid®, Aciphex®, Protonix® and Nexium® and participated in post-launch educational activities related to each of these drugs. I have been a member of small groups of experts who assessed and interpreted clinical data associated with each of these agents prior to their launch. I am therefore familiar with the process for the release of a new drug in the United States, and new PPIs, in particular.

90. The process for release or launch of a new PPI comprises several steps, which I discuss below in the usual order in which they occur.

91. When Phase II clinical studies (designed to evaluate clinical efficacy) show promising results, experts are consulted to plan Phase III studies (Phase III studies are also called regulatory studies and consist of two large randomized controlled trials conducted in multiple centers in the United States to demonstrate efficacy of the drug. These have been conducted with esomeprazole magnesium). It is at this point, when the relevant scientific community becomes aware of a potential new therapeutic agent. When Phase III trials are conducted, practicing gastroenterologists and experts perform the study, which further increases awareness of the drug. Other physicians also participate in the large Phase III trials and also become aware of the studies and data. As the data of the Phase III trials become available and are prepared for

submission to the FDA, the study data are presented at major U. S. scientific meetings (*e.g.* American Gastroenterological Association or American College of Gastroenterology) and the broader gastroenterology community becomes aware of the data. Prior to launch, advisory board meetings are scheduled with groups of gastroenterologists to obtain their opinions and to prepare a marketing strategy for the new Drug. At this time, a brand name is chosen for the drug, tested in focus groups and reviewed by the FDA (to avoid l similarities with other approved agents). Speaker bureaus are also established to educate primary care physicians, physician assistants and others regarding the new drug in advance of the launch and shortly after launch.

V. HANMI'S ESOMEPRAZOLE STRONTIUM

92. Counsel for AstraZeneca has informed me that Hanmi received approval for Esomeprazole Strontium delayed release capsules on August 6, 2013. I have received a copy of the FDA approval letter.[120] I was unaware of the approval of Hanmi's product by FDA or a planned launch of a new PPI, prior to being informed by AstraZeneca's counsel and receiving the FDA approval letter. I have not heard or seen any information about the Hanmi product or esomeprazole strontium. I have also not heard any discussion of this agent among my colleagues and fellow gastroenterologists.

93. I find news of an imminent launch[121] of this esomeprazole product highly unusual. My colleagues and I would expect to have had significant knowledge about this product well before launch. None of the typical steps associated with the launch of a new PPI have taken place and I have no knowledge that anyone in the scientific community, in particular

[120] FDA Approved Drug Products with Generic Equivalence Evaluations ("Orange Book"), available at http://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm

[121] http://www.globalpost.com/dispatch/news/yonhap-news-agency/130807/us-fda-oks-sale-s-koreas-improved-version-nexium

gastroenterologists and the leaders in our community, has any awareness of this product. I am not aware of any presentations at scientific meetings and meetings of gastroenterologists, where I would expect news of a new therapeutic product to be prescribed by gastroenterologists to be announced. I attended the 2013 Digestive Disease Week ("DDW") conference in Orlando, Florida., which is a major annual conference drawing gastroenterologists from all over the world, leaders in the field, along with representatives from pharmaceutical companies and healthcare organizations. I acquired no awareness of Hanmi or an esomeprazole strontium product at that meeting. In view of an expected launch, I would have expected high exposure of a new product at this highly prominent meeting.

94. To my knowledge, there have been no clinical studies of esomeprazole strontium, publications of these studies and no expert panels or advisory boards related to this drug.

95. I note from the FDA approval letter that Hanmi's drug has been approved as a new brand but has no brand name. I understand from the FDA approval letter that Hanmi's product will be marketed as esomeprazole strontium delayed release capsules.

VI. EFFECT OF ESOMEPRAZOLE STRONTIUM LAUNCH

96. Switching patients from a drug that is working for them can have consequences for the patient and for society. In accordance with managed care formulary guidelines, Nexium® has occasionally been excluded by managed care organizations and a switch has been forced to other agents, to save the managed care organization money. When one of the largest managed care providers in the USA attempted this, it had the opposite effect paradoxically

raising costs because the new treatment was ineffective in treating the patient.[122] Therefore the arrival of any new agent that could change existing therapies either deliberately due to a forced managed care change or accidentally due to confusion with pre-existing therapy (with Nexium® in this case) is a cause for concern on the part of patients and the physicians treating them.

A. Physicians

97. The lack of clinical study data for esomeprazole magnesium, the lack of pre-launch education of leaders of the gastroenterology community and the lack of pre-launch notice to physicians demonstrates that a great majority of physicians will not become aware Hanmi's esomeprazole strontium product until it reaches the market.

98. An unpublicized introduction of esomeprazole strontium or any new drug will likely be upsetting to many clinicians. The lack of pre-launch communication with physicians and the lack of published scientific information makes it likely that clinicians will first learn of esomeprazole strontium from a pharmacist or patient.

99. Given the lack of information Hanmi has disseminated about its product, the risk of confusion here is very high. Patients and clinicians are likely to be caught off-guard by the presence of an esomeprazole alternative particularly because we do not know its clinical efficacy related to Nexium®.

100. The lack of pre-launch information about Hanmi's esomeprazole strontium product combined with its lack of a brand name will create confusion about the relationship between esomeprazole magnesium (Nexium®) and esomeprazole strontium. Without any clinical data or information on esomeprazole strontium, most physicians (and

[122] Alemayehu et al, "Esomeprazole formulary exclusion: impact on total health care services use and costs", *Postgraduate Medicine*, (2012), 124(3), 149-63.

gastroenterologists) will not know the difference between Nexium® and esomeprazole strontium and are likely to confuse the two. As noted above, switches in agents can have unfortunate effects on clinical outcomes in patients and a deterioration in their condition. The absence of a brand name may create the perception that esomeprazole strontium is generic Nexium® or that AstraZeneca is either involved or responsible for the new PPI.

101. I performed an online search on August 18, 2013 to identify any information relating to the launch of esomeprazole strontium. I identified several press reports characterizing esomeprazole strontium as an "improved Nexium" while Hanmi's website states that it is a generic drug. Although not all these reports appear to be statements directly from Hanmi, I do believe that the public representations of esomeprazole strontium are indicative of the mixed message that will be delivered to patients and physicians, when Hanmi's esomeprazole strontium enters the market.

102. Many physicians will also consult the product insert (label) when they first encounter a new drug. Under these circumstances, the label for Hanmi's esomeprazole strontium capsules will likely enhance the confusion.

103. Hanmi's esomeprazole strontium label contains only limited pharmacological study of esomeprazole strontium. Hanmi's label does not contain any study evaluating esomeprazole strontium in patients with GERD. The only studies in Hanmi's label directed toward clinical endpoints use **esomeprazole magnesium (Nexium®)**. The data presented in Hanmi's label therefore cannot demonstrate whether the drug is equivalent, superior or inferior to Nexium®. The label states "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in

practice. The safety of esomeprazole strontium has been established from adequate and well-controlled studies of esomeprazole magnesium. " To a clinician and scientist, this is both confusing and lacks transparency. As this is a new drug and approved under a new drug application, we would want to see safety and efficacy data of that drug before making any prescribing decision

104. Hanmi's pricing of its esomeprazole strontium capsules will likely increase confusion. If Hanmi prices its esomeprazole strontium capsules as a generic and gains a favorable position on managed care formularies compared to Nexium®, pharmacies and healthcare plans will use various cost-control mechanisms to shift prescriptions from Nexium® to the lower-cost Hanmi product. These mechanisms will likely emphasize "esomeprazole" or the "similarities" of esomeprazole strontium to Nexium® (esomeprazole magnesium) which remain unproven. This will further enhance the incorrect perception that Nexium® and esomeprazole strontium are either the same (Pharmaceutically Equivalent) or Therapeutically Equivalent.

105. There is therefore a high likelihood that a launch of esomeprazole strontium delayed release capsules will create confusion among practicing physicians and gastroenterologists who are likely to prescribe PPIs.

B. Patients

106. Given the lack of information Hanmi has disseminated about its product, the risk of patient confusion regarding the two compounds is certain. Patients will likely confuse esomeprazole strontium with esomeprazole magnesium (Nexium®), because both products will contain "esomeprazole" on their labeling, Patients will not know that the two compounds have not been compared and have not been shown to be clinically equivalent. They will also not know

that the rigorous clinical trials conducted with Nexium® have not been conducted with esomeprazole strontium and that safety and efficacy are inferred from the extensive research conducted on Nexium® but are not demonstrated for the new compound. To make an informed decision to choose a pharmaceutical agent, patients need to be aware of this.

107. As discussed above, Nexium® provides a number of clinical advantages compared to omeprazole or other PPIs. Many patients receiving Nexium® have previously failed on other PPI. Patients successfully treated on Nexium® would have no reason to switch to esomeprazole strontium, particularly if those patients had been switched to Nexium® after one or more treatment failures. A forced switch of these patients from Nexium® to esomeprazole strontium could upset the patients' established course of treatment and lead to recurrent symptoms and clinical problems as have occurred with other mandated switches by managed care organizations in the past.

108. I declare under penalty of perjury under the laws of the State of Massachusetts that the foregoing is true and correct and that this Declaration was executed this 20th day of August, 2013, at Milwaukee, Wisconsin.

NIMISH VAKIL, M.D. FACG, AGAF, FASGE